The Office Action

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected, under 35 U.S.C. § 112, first paragraph. Claims 10-13, 15-29, 36, and 40-42 also stand rejected under 35 U.S.C. § 112, second paragraph. Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected under 35 U.S.C. § 102(e). Each of these rejections is addressed as follows.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected, under 35 U.S.C. § 112, first paragraph, on the basis that the disclosure in applicants' specification (1) is not commensurate in scope with the claimed invention and (2) fails to provide a written description of the claimed invention. For the following reasons, each of these rejections is respectfully traversed.

Scope of Enablement

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected under § 112, first paragraph based on the assertion that the teachings of applicants' specification is not commensurate in scope with the present claims. The Office Action states:

> Applicant has not provided specific guidance for isolation of other structurally related nucleic acid sequences which encode disease resistance polypeptides. The basis for doubting that structurally related nucleic acids would necessarily confer disease resistance in plants is that the ankyrin repeat motif has been identified in many different functionally unrelated proteins. Hence, structural relatedness alone is not sufficient basis to predict functional relatedness. Applicant's teaching of screening transformed plants for enhanced disease resistance is merely an invitation to experiment, and does not constitute specific guidance for isolation of structurally and functionally related DNAs to the discloses *Arabidopsis NPR1* cDNA.

For the following reasons, applicants respectfully traverse this ground of the rejection.

As an initial matter, applicants note that if one skilled in the art wished to isolate structurally-related nucleic acid sequences which encode disease resistance polypeptides, they would simply use applicants' disclosed nucleotide sequences as a probe, in combination, with conventional methods, such as hybridization or PCR amplification. To this end, applicants, in their specification, outline general methods useful for identifying and isolating DNAs encoding additional structurally-related resistance gene sequences, for example, at page 50-53, and also provide exemplary oligonucleotide primers for use in connection with these methods. These approaches require only standard application of routine molecular methods. Accordingly, as noted in previous correspondence, there is no basis for concluding that one skilled in the art, equipped with applicants' sequences and standard methods known in the art, would not be able to isolate a reasonable number of structurally-related nucleic acid sequences which encode resistance genes falling within the scope of the present claims.

Furthermore, structural relatedness is indeed a sufficient means to isolate functionally related species in the case of *NPR1* without undue experimentation. As evidence of this assertion, applicants point out that, subsequent to the filing of their patent application, researchers identified at least three gene sequences from apple that are not only structurally, but functionally related to the *NPR1* acquired resistance gene. On this point, the Examiner's attention is directed to the publication of Jin et al., entitled "Cloning and characterization of *Arabidopsis NPR1*-homologous genes from apple (*Malus pumila)*" (http://courses.washington.edu/bot427/genomeTF.pdf; Abstract 152, *11th International Conference on Arabidopsis Research,* held at the University of Wisconsin-Madison, June 24-28, 2000; copy attached as Exhibit A). Here Jin, using the coding region of applicants' *Arabidopsis NPR1* gene as a probe, screened an apple cDNA library and isolated several clones containing genes structurally related to *NPR1*. This

results confirms that the guidelines provided by the teachings of applicants' disclosure are effective for acquired resistance gene isolation.

Moreover, by overexpressing one of these genes, *MpNPR1-1*, in the *Arabidopsis npr1* disease-susceptible mutant, Jin established that the apple resistance gene "partly recovered" the disease resistant phenotype of *PR-1* gene induction, indicative of the function of the apple gene as not only an *NPR1* homolog, but also a resistance gene. Such data strongly corroborate applicants' claim that additional gene sequences may be isolated from a variety of sources using standard techniques that were known in the art and that were useful for practicing the methods of the claimed invention. Indeed, contrary to the conclusions made in the Office Action that applicants' teaching is "merely an invitation to experiment," the teachings of applicants' disclosure has been shown to be effective for gene isolation of additional structurally- and functionally- related resistance genes from a plant other than *Arabidopsis*.

As further evidence on this point, applicants also direct the Examiner's attention to the accompanying Declaration of Xinnian Dong, a co-inventor on this application. In this declaration, Dr. Dong describes experimental results demonstrating that overexpression of the dicot *Arabidopsis NPR1* gene, in the monocot rice, leads to enhanced disease resistance to *Xanthomonas oryzae* pv. *oryzae* (Xoo), the causative agent of rice blight. Dr. Dong further explains that since transgenic rice plants overexpressing the *Arabidopsis NPR1* gene displayed enhanced disease resistance, it is not unreasonable to conclude that rice shares with *Arabidopsis* a similar disease resistance pathway mediated by *NPR1*. Moreover, Dr. Dong notes that such results substantiate applicants' teaching that resistance genes, like the *Arabidopsis NPR1*, exist in other plants such as rice, and encode resistance proteins functionally equivalent to the *Arabidopsis* NPR1 protein.

In view of the aforementioned evidence, there is no reason to doubt the objective truth of the statements made in applicants' specification that are relied upon for enabling

support. Withdrawal of the § 112, first paragraph rejection, based on failing to provide a disclosure commensurate with the claims is respectfully requested.

Written Description

Claims 1-29, 36, and 40-42 stand rejected under 35 § U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention. In essence, the Office's rejection is based on the following proposition:

> Applicant has not described another disease resistance polypeptide comprising an ankyrin repeat, and hence it is not clear that a genus of disease resistance polypeptides comprising an ankyrin repeat even exists.

For the following reasons, this basis of the § 112 rejections is respectfully traversed.

With respect to the existence of additional resistance polypeptides, applicants' again direct the Examiner's attention to the Jin publication and the Dong Declaration that provide compelling evidence for the existence of genes that are structurally and functionally related to those described and claimed in applicants' specification. Given such proof, there is no reason for the Office to doubt the existence of a new family of resistance polypeptides as described in applicants' specification.

Turning to the issue that applicants have not described a representative number of species of the claimed genus, applicants first point out that "[r]epresentative examples are not required by the statute and are not an end in themselves." *In re Robins,* 429 F.2d 452,457, 166 U.S.P.Q. 552, 555 (C.C.P.A. 1970). Rather, applicants' specification "must 'convey clearly' to those skilled in the art to whom it is addressed ... the information that [the inventor] has invented the specific subject matter later claimed." *Martin v. Mayer,* 853 F.2d 500, 505, 3 U.S.P.Q.2d 1333, 1337 (Fed. Cir. 1987). Moreover, a written description of nucleic acid molecules may be satisfied by "recitation of structural features

common to members of the genus." *Regents of the Univ. of California v. Eli Lilly and Co.,* 119 F.3d 1559, 1569, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997) (footnote omitted).

As noted in previous correspondence, applicants have plainly met these standards. Indeed, the present specification would certainly indicate to one of ordinary skill in the art that applicants discovered a family of related nucleic acid molecules encoding ankyrin repeat-containing disease resistance polypeptides, as currently claimed.

On this point, the Examiner's attention is again directed to applicants' specification, for example, at page 6 (lines 14) – page 7 (line 21), and in particular at page 7 (lines 19-21), where applicants describe, with particularity, the claimed class of acquired resistance genes. Based on this description and other statements contained within the specification, one skilled in the art, like Jin who isolated apple NPR homologs using the *Arabidopsis NPR1* gene, would recognize and appreciate that applicants had indeed invented the scope and content of the presently claimed invention. On this basis alone, the written description rejection should be withdrawn.

In addition, applicants further described the claimed class of acquired resistance genes in view of their shared characteristic ankyrin repeats. See for example, applicants' specification at page 6 (lines 11-12) and page 43 (line 28) – page 44 (line 9). Indeed, applicants submit that, even though the claimed invention is exemplified by the *Arabidopsis NPR1* and *Nicotiana glutinosa NPR1* homolog described in the present specification, one of skill in the art reading this specification would have readily recognized that these genes were merely provided for the purpose of illustrating the invention and that applicants' invention included <u>any</u> acquired resistance gene encoding a disease resistance polypeptide having an ankyrin repeat. It is this description also that clearly conveys applicants' invention to those persons of skill in the art. This description also allows the skilled worker to identify and recognize other species falling within the present claims.

Thus, there can be no question that applicants were in possession of the claimed genus at the time their application was filed, and that one skilled in the art would recognize applicants' disclosure as a description of the invention defined by the present claims. As a result, applicants' specification clearly satisfies the written description requirement, as set forth by the case law, and applicants request reconsideration and withdrawal of this basis for the § 112 rejection.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 10-13, 15-29, 36, and 40-42 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 10-12 were deemed indefinite in reciting the phrase "specifically hybridizes to" because the phrase is indefinite. The Office Action, at page 6, states:

> [T]he scope of the claimed invention encompasses nucleic acid molecules which would hybridize at low stringency conditions or those which would hybridize at high stringency conditions. Also because the specification provides multiple definitions, and/or uses of the language "for example" or "may include," applicant has not provided a clear definition of "low stringency" or of "high stringency."

This rejection is respectfully traversed.

Applicants point out that the meaning of "specifically hybridizes" is made clear by applicants' specification. At page 12 (lines 1-3), the specification states:

> By "specifically hybridizes" is meant that a nucleic acid sequence is capable of hybridizing to a DNA sequence under at least low stringency conditions as described herein, and preferably under high stringency conditions, also as described herein."

As an initial matter, based on this definition, it is clear that "specifically hybridizes" refers to both low and high stringency conditions. Furthermore, applicants' specification, at pages 51 (line 12) - 52 (line 3), describes exemplary high and low stringency hybridization conditions. For example, with respect to exemplary high stringency conditions, the specification, at page 51 (lines 12-21) states:

> In one particular example of this approach, related AR sequences having greater than 80% identity are detected or isolated using high stringency conditions. High stringency conditions may include hybridization at about 42 °C and about 50% formamide, 0.1 mg/mL sheared salmon sperm DNA, 1% SDS, 2X SSC, 10% Dextran sulfate, a first wash at about 65 °C, about 2X SSC, and 1% SDS, followed by a second wash at about 65 °C and about 0.1X SSC. Alternatively, high stringency conditions may include hybridization at about 42 °C and about 50% formamide, 0.1 mg/mL sheared salmon sperm DNA, 0.5% SDS, 5X SSPE, 1X Denhardt's, followed by two washes at room temperature and 2X SSC, 0.1% SDS, and two washes at between 55-60 °C and 0.2X SSC, 0.1% SDS.

And, with respect to low stringency conditions, the specification, at pages 51 (line 22) - 52 (line 2), states:

> In another approach, low stringency hybridization conditions for detecting AR genes having about 40% or greater sequence identity to the AR genes described herein include, for example, hybridization at about 42 °C and 0.1 mg/mL sheared salmon sperm DNA, 1% SDS, 2X SSC, and 10% Dextran sulfate (in the absence of formamide), and a wash at about 37 °C and 6X SSC, about 1% SDS. Alternatively, the low stringency hybridization may be carried out at about 42 °C and 40% formamide, 0.1 mg/mL sheared salmon sperm DNA, 0.5% SDS, 5X SSPE, 1X Denhardt's, followed by two washes at room temperature and 2X SSC, 0.1% SDS and two washes at room temperature and 0.5X SSC, 0.1% SDS.

Moreover, applicants' specification, at page 49 (lines 14-20), describes the following additional low stringency hybridization conditions:

> Hybridization was performed at 37 °C in 40% formamide, 5X SSC, 5X Denhardt, 1% SDS, and 10% dextran sulfate. The filters were washed in 2X SSC for fifteen minutes at room temperature and 2X SSC, 1% SDS for thirty minutes at 37 °C.

Given applicants' definition of the phrase "specifically hybridizes," in view of the art-recognized exemplary standard low and high stringency hybridization conditions set forth in applicants' specification, a skilled worker would readily appreciate the meaning of this phrase and the scope of the claimed invention. Clearly, various hybridization conditions can be employed to arrive at the same level of stringency, and this breadth should not be equated with indefiniteness. Moreover, applicants' phrase "specifically hybridizes" is entirely consistent with art recognized procedures involving hybridization methodologies used to determine whether complementary polynucleotides (e.g., DNA:DNA, RNA:RNA, or RNA:DNA) form double helices, and the use of such methods for identifying genes that are nonidentical but related, structurally and functionally, to a particular gene. Accordingly, the skilled worker would readily understand that low stringency hybridization methodologies represent a powerful use of DNA technology that allows for distantly related genes with related functions to be identified.

Finally, applicants' again point out that recitation of one particular format for high or low stringency hybridization conditions would unfairly limit applicants' claims and is more than required by the MPEP and the case law. See, for example, § 2173.04 of the MPEP (July 1998) ("Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter

embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.") and *Miles Laboratories v. Shandon, Inc.*, 997 F.2d 870, 875, 27 U.S.P.Q.2d 1123, 1126 (Fed. Cir. 1993) ("If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more . . . The degree of precision necessary for adequate claims is a function of the nature of the subject matter."). Reconsideration on this issue is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 1, 2, 4-13, 15-29, 36, and 40-42 stand rejected under 35 U.S.C. § 102(e) as anticipated Ryals (U.S. Patent No. 6,091,004). For the following reasons, applicants respectfully disagree.

Applicants' claimed invention is generally directed to "isolated nucleic acid molecules," which is defined at page 11 (lines 20-27) as follows.

> DNA that is free of the genes which, in the naturally-occurring genome of the organism from which the DNA of the invention is derived, flank the gene. The term therefore includes, for example, a recombinant DNA that is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or that exists as a separate molecule (for example, a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequence (emphasis added).

In view of this definition, Ryals does not anticipate applicants' claimed invention. The Ryals priority document (copy enclosed), provisional application no. 60/020,272,

filed June 21, 1996, fails to disclose a DNA molecule free of other genes from the genome encoding an acquired resistance gene, as is claimed by applicants. Accordingly, Ryals does not represent prior art to applicants' invention, and the § 102 rejection may be withdrawn.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is respectfully requested. Enclosed is a petition to extend the period for replying for three months, to and including February 8, 2001.

If there are any charges or credits, please apply them to deposit account number 03-2095.

Respectfully submitted,

Date: 8 February 2001

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EXHIBIT A

152 Cloning and characterization of *Arabidopsis NPR1*-homologous genes from apple (*Malus pumila*)

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The *Arabidopsis thaliana NPR1* gene (nonexpressor of pathogenesis-related genes, also called *NIM1*) is a key regulator of systemic acquired resistance (SAR) against a broad spectrum of pathogens. The *npr1* mutant is impaired in the ability to mount a SAR response even after treatment with salicylic acid (SA) or benzothiadiazole (BTH). Overexpression of *NPR1* confers enhanced resistance to multiple pathogens. To determine whether an *NPR1* ortholog exists in apple, and whether this gene can be used to enhance resistance against the devastating apple fire blight pathogen *Erwinia amylovora*, we screened an apple cDNA library constructed from apple seedlings treated with BTH. The coding region of the *A. thaliana NPR1* gene was used as a probe in this screen. From 2 million plaques, we obtained 10 positive clones that were subsequently classified into 3 groups based on restriction enzyme analysis. Three representative clones were sequenced and designated *MpNPR1*-1, *MpNPR1*-2 and *MpNPR1*-3, respectively. The deduced amino acid sequence of *MpNPR1*-1 had 72% identity to that of *MpNPR1*-2 and 90% identity to that of *MpNPR1*-3. All of them shared about 35% amino acid identity with the *A. thaliana* NPR1. RNA blot analysis indicated that only *MpNPR1*-1 was induced in apple seedlings treated with BTH. Overexpression of *MpNPR1*-1 in the *A. thaliana npr1* mutant partly recovered the *PR-1* gene induction upon BTH treatment, suggesting that *MpNPR1*-1 is likely to be an apple ortholog of the *A. thaliana NPR1* gene. This work provides the basis for future genetic engineering of disease resistance in apple and possibly other pome fruits.